Addition of cyclophosphamide to steroids provides no benefit compared with steroids alone in treating adult patients with severe Henoch Schönlein Purpura

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Henoch Schönlein Purpura (HSP) is a common disease in children, usually associated with a good prognosis. In adults there are no prospective studies concerning its prognosis or treatment, especially in cases of severe visceral involvement. Here we compared steroid therapy without or with cyclophosphamide co-treatment in adults with severe HSP in a 12-month, multi-center, prospective, open-label trial that treated 54 adults with biopsy-proven HSP including proliferative glomerulonephritis and severe visceral manifestations. All received steroids; however, 25 were randomized to also receive cyclophosphamide. The primary endpoint that occurred in three patients in each group was complete disease remission defined as zero on the Birmingham Vasculitis Activity Score with no persistent or new clinical and/or biological vasculitis at 6 months. No patient had active visceral involvement. The secondary endpoints were renal outcome, deaths, and adverse events at 12 months. Renal function, proteinuria, safety data, incidence of diabetes, and severe infections were similar between the two groups. At the last follow-up, renal function remained stable. The small population size of our study does not permit definitive conclusions; however, we suggest that treatment of adults with severe HSP by adding cyclophosphamide provides no benefit compared with steroids alone.

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Henoch Schönlein Purpura (HSP) is the most frequent vasculitis in childhood. HSP occurs less frequently in adults, but is usually more severe than that in children.[1,2] Gastrointestinal and pulmonary involvement can be life-threatening, and HSP nephritis with severe endo- and/or extra-capillary proliferation on biopsy can progress to end-stage renal disease in up to 30% of patients during long-term follow-up.[3,4]

Management of HSP remains controversial. In children, various treatment regimens have been proposed in cases of severe digestive involvement or nephritis, including cortico-steroids, azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, and recently, rituximab.[5–9] Results have been conflicting. In adults, however, no randomized study has been undertaken to evaluate the efficacy of any treatment modality.

The aim of this prospective, randomized study was to compare the efficacy and safety of steroids alone or in combination with pulse cyclophosphamide for the treatment of severe adult HSP.

RESULTS

Fifty-four patients were recruited in 31 centers in France between September 2002 and September 2006, and were randomized to receive steroids alone (CS) ($n=29$) or steroids and cyclophosphamide (CYS) ($n=25$) (Figure 1). Long-term follow-up continued to 1 April 2009, with follow-up data being obtained for 20 patients in the CS group (including two patients evaluated before death) and 20 patients in the CS + CYC group (data were missing for one patient in addition to those who were deceased and lost to follow-up), with a median follow-up of 60.9 months (first quartile to third quartile (Q1–Q3): 47.4–69.7 months) and 59.8 months (Q1–Q3: 49.2–68.0 months), respectively.

Clinical findings at baseline

The demographic and baseline disease characteristics are presented in Table 1. Age at study entry ranged from 18 to 84 years. The two treatment groups were well-balanced except

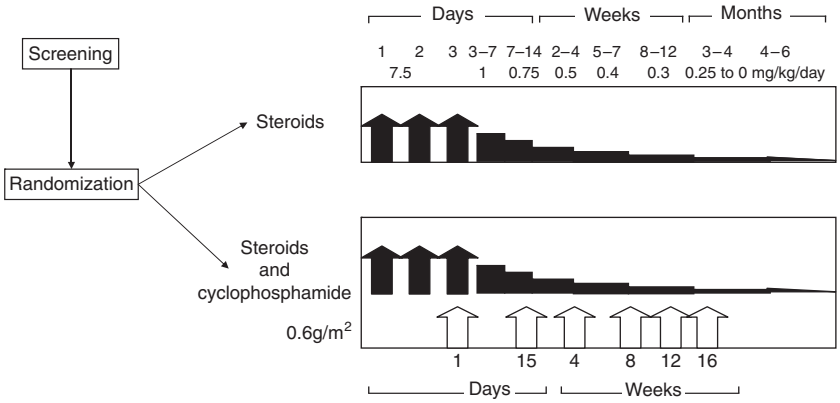


Figure 1 | Patient disposition. All patients received the allocated treatment. Patients shown as 'not evaluated' did not attend the relevant study visit. The last follow-up took place at a median of 61 months in the CS group and at 60 months in the CS + CYC group.

Table 1 | Demographic, clinical, and biological characteristics at baseline

	Steroids	Steroids+cyclophosphamide	*P*-value
n	29	25	
Sex, male, *n* (%)	17 (58.6%)	17 (68.0%)	0.66
Mean (s.d.) age (years)	60.7 (11.0)	52.8 (18.5)	0.01
Recent history of infection, *n* (%)	12 (41.4%)	11 (44.0%)	
Comorbidities			
Hypertension, *n* (%)	15 (51.7%)	6 (24.0%)	0.04
Diabetes, *n* (%)	7 (24.1%)	3 (12.0%)	0.31
Physical examination			
Blood pressure (mm Hg), mean	134/77	130/74	
Mean (s.d.) weight (kg)	79.2 (17.4)	72.0 (13.8)	
Skin lesions	28 (96.6%)	24 (96.0%)	
Type: purpura	26/28 (92.9%)	23/24 (95.8%)	
Necrosis: bullous, *n* (%)	11/28 (39.3%)	8/24 (33.3%)	
Gastrointestinal involvement, n (%)	16 (55.2%)	13 (52%)	
Moderate abdominal pain, *n* (%)	8 (27.6%)	5 (20.8%)	
Severe involvement, *n* (%)	8 (27.6%)	7 (29.2%)	
Joint manifestation, *n* (%)	16 (55.2%)	16 (64.0%)	0.70
Other organ involvement, *n* (%)	2 (7.1%)	3 (13.0%)	0.90
Biological tests			
CRP (mg/l), median (range)	28 (3–193)	28 (0–222)	
Albumin (g/l), median (range)	28 (13–37)	30 (13–48)	
Creatinine (μmol/l), median (range)	110 (53–668)	88 (61–903)	0.22
eGFR (ml/min), median (range)	60 (10–125)	76 (9–132)	0.36
eGFR < 60 ml/min, *n* (%)	14 (48.3%)	9 (36.0%)	
Proteinuria (g/24 h), median (range)	3.2 (0; 21)	3.6 (0; 12)	
Proteinuria ⩾1 g/day, *n* (%)	21 (72.4%)	22 (88%)	
Hematuria ⩾10 RBC/mm^3, *n* (%)	23 (88.5%)	22 (95.7%)	
Renal biopsies	24	24	
Glomerular score (class), *n* (%)			
Mesangiopathic GN (1)	1 (4.2%)	0 (0%)	
Focal and segmental GN (2)	4 (16.7%)	4 (16.7%)	
Endocapillary proliferative GN (3)	10 (41.7%)	13 (54.2%)	
Endo/extra-capillary proliferative GN (4)	9 (37.5%)	7 (29.2%)	
Global glomerular sclerosis, median (range)	1 (0–4)	1 (0–3)	
Interstitial fibrosis (%), median (range)	13 (0–40)	0 (0–40)	
None–mild (<25%), *n*	16	21	0.17
Moderate (25–50%), *n*	8	3	
Severe (>50%), *n*	0	0	
Vascular disease, *n* (%)	17 (70.8%)	14 (58.3%)	
Skin biopsies	23	21	
Leukocytoclastic vasculitis, *n* (%)	23 (100.0%)	18 (85.7%)	

Abbreviations: CRP, C-reactive protein; eGFR, estimated renal function; GN, glomerulonephritis; *n*, number of patients.
The two treatment groups were well-balanced except, due to the lower number of recruited patients, for age and hypertension.

for age, hypertension, and disease activity (assessed by Birmingham Vasculitis Activity Score (BVAS)), due to the low number of patients recruited. Indeed, the patients in the CS + CYC group were younger, less hypertensive, had lower vasculitis disease activity, and better renal function. The most frequent clinical manifestation in all HSP patients was purpura, which was predominantly observed on the lower limbs. Purpura was necrotic or bullous in 19/52 patients (36.5%), with similar incidence in each cohort. Joint manifestations were present in 59.3% of the patients (32/54), including 16 patients in each group (Table 1). Fever and/or alteration of clinical status were observed in 50% of the patients at baseline (26/54): 58.3% (17/29) in the CS group versus 11/25 (44.0%) in the CS + CYS group. Gastrointestinal involvement was present in 29 patients (53.7%) overall, and each of these patients experienced abdominal pain. Three patients in the CS group and two in the CS + CYC group had gastrointestinal hemorrhage. Bowel ischemia was present in five CS patients and eight CS + CYC patients. One CS patient and two CS patients had severe gastrointestinal involvement without nephritis.

Renal findings at baseline

At baseline, as shown in Table 1, median creatinine was 110 μmol/l (range 53–668 μmol/l) in the CS group and 88 μmol/l (61–903 μmol/l) in the CS + CYC cohort. The estimated glomerular filtration rate (eGFR) (Cockroft–Gault) was 60 ml/min (10–225 ml/min) versus 76 ml/min (9–132 ml/min), respectively. Fourteen patients (48%) in the CS group and nine (36%) in the CS + CYC group had eGFR < 60 ml/min at baseline, with two CS patients and three CS + CYC patients requiring dialysis.

A similar proportion of patients in each group had proteinuria > 0.2 g/day (CS, 27/29 (93%); CS + CYC, 24/25 (96%)). Proteinuria ⩾ 1 g/day was present in 21/29 CS patients (72%) and 22/25 CS + CYC patients (88%). Of note, 10/29 (34%) CS patients versus 11/24 (46%) CS + CYC patients presented with nephrotic syndrome.

Hypertension was present in 15/29 (52%) CS patients and 6/25 (24%) CS + CYC patients. Of these, 19 patients received renin–angiotensin system blockers (CS, 11; CS + CYC, 8).

Renal biopsy results at baseline were available for 24 patients in each group. The two groups were well-matched with respect to histological findings, exhibiting a similar degree of glomerulosclerosis, tubular atrophy, interstitial fibrosis, and vascular disease. Diffuse endocapillary proliferative glomerulonephritis (GN) (class-3 and 4) was observed on 79.2% of the biopsies from the CS group and 83.4% of the biopsies from the CS + CYC group.

Primary endpoint

As shown in Table 2a, the BVAS improved substantially in both the groups from day 0 (CS, median 28 (range 12–48); CS + CYC, 20 (7–45); $P = 0.02$) to month 6 (M6) (CS, 12 (0–45); CS + CYC, 9 (0–28); $P = 0.41$). The median decrease in the BVAS from day 0 to M6 was −17 (range −26; −7) in the CS group versus −12 (−20; −6) in the CS + CYC group ($P = 0.14$). The primary endpoint, a BVAS of zero with no persisting or new clinical and/or biological vasculitis activity at M6, occurred in three patients in each group (CS, 3/29

Table 2 | Clinical and biological endpoints

	Steroids	Steroids+cyclophosphamide	*P*-value
(a) **Primary endpoints**[a]			
n	29	25	
BVAS			
Score at day 0, median (range)	28 (12–48)	20 (7–45)	0.02
BVAS score=0 at month 6, *n*	3 (10)	3 (12)	1.00
Score at month 6, median (range)	12 (0–45)	9 (0–28)	0.41
Change from day 0 to month 6, median (range)	−17 (−38; 1)	−12 (−33; 9)	0.14
Improvement (< −1)	26	22	
Unchanged (−1–1)	3	2	
Worsening (> 1)	0	1	
(b) **Secondary endpoints**[b]			
HSP nephritis at month 12	29	25	
Blood pressure > 125/75 mm Hg, *n* (%); *n*=19/16	15 (79%)	13 (81%)	0.99
Creatinine (μmol/l), median (range); *n*=19/16	98 (79–123)	93 (74–134)	0.81
eGFR (ml/min), median (range); *n*=19/15	70 (17–123)	77 (18–115)	0.52
eGFR < 60 ml/min, *n* (%) *n*=19/15	8 (42%)	5 (33%)	1.00
Proteinuria (g/day), median (range); *n*=15/15	0.3 (0–3.6)	0.6 (0–2.0)	0.76
Proteinuria ⩾ 1 g/day, *n* (%)	4 (27%)	3 (20%)	
Hematuria ⩾ 10 RBC/mm^3, *n* (%); *n*=11/12	3 (27%)	5 (42%)	0.67
RAS blockers, *n* (%); *n*=19/17	14 (74%)	12 (71%)	1.00
Renal function improvement > 50%, *n* (%); *n*=19/16	4 (21%)	1 (6%)	0.35
End-stage renal disease, *n*	1	1	

Abbreviations: BVAS, Birmingham Vasculitis Activity Score; eGFR, estimated renal function; *n*, number of patients; RAS, renin-angiotensin system; RBC, red blood cells.
[a]Disease activity at baseline, as assessed by the BVAS, was lower in the CS+CYC group. At month 6, no patient showed active visceral involvement.
[b]HSP nephritis. At month 12, renal function and proteinuria were not different in both the groups.

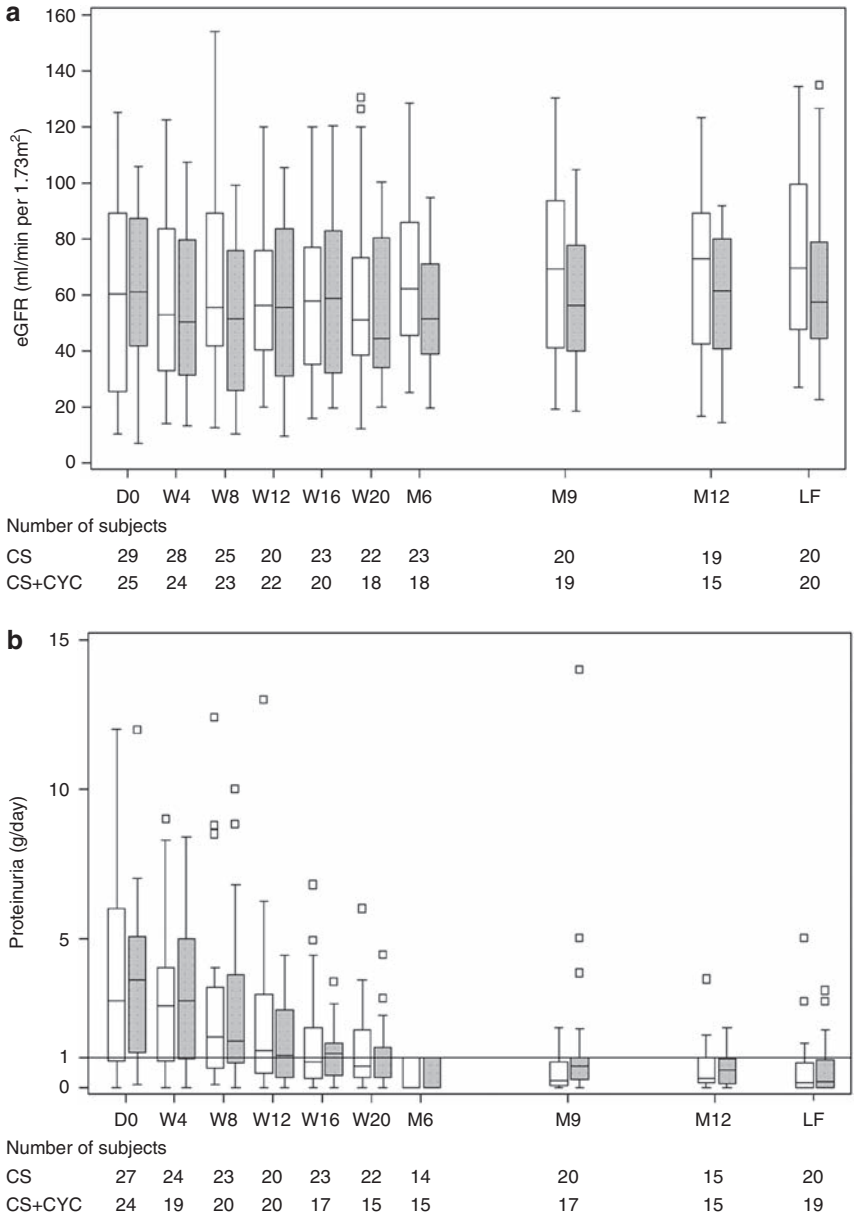


Figure 2 | Renal outcome. (**a**) eGFR (Cockcroft–Gault) and (**b**) daily proteinuria (g/day) in patients receiving steroids alone (CS, open boxes) or steroids and cyclophosphamide (CS + CYC, filled boxes) from day 0 (D0) until the last follow-up (LF).

(10.3%); CS + CYC, 3/25 (12.0%); $P = 1.00$). Logistic regression modeling confirmed the absence of difference in the incidence of the primary endpoint between the treatment groups after adjustment for age, BVAS, and hypertension at study entry.

Some patients still experienced clinical manifestations at M6, but without any visceral involvement. Six patients in the CS + CYC group presented with skin purpura at M6, including one case of necrotic and bullous purpura. Other manifestations at M6 included persisting arthralgia in three patients and minor abdominal pain in one patient, all withi the CS + CYC group. At the end of the follow-up no patients showed any extra-renal manifestation.

Renal outcome

As shown in Table 2b, renal outcome was similar between the two groups even after stratification according to baseline parameters, including histopathological criteria.

Renal function improved to a similar extent in both the groups by month 12 (M12), with eGFR increasing by $>50\%$ in 4/19 CS patients (21%) and 1/16 (6%) CS + CYC patients (Figure 2a). By M12, 8/19 (42%) patients in the CS group versus 6/16 (38%) patients in the CS + CYC group had eGFR <60 ml/min ($P = 0.33$). One patient in each group reached end-stage renal disease, with a delay of 8 and 12 weeks, respectively. Even though the number of patients exceeding 48 months of follow-up was relatively small, it

should be emphasized that renal function remains stable at the last follow-up. At the last follow-up, median serum creatinine was 103 µmol/l (range: 51–390 µmol/l) in the CS arm versus 90 µmol/l (range: 50–219 µmol/l) in the CS + CYC arm ($P = 0.32$), and median eGFR was 69 ml/min (range: 27–120 ml/min) versus 72 ml/min (range: 28–150 ml/min), respectively ($P = 0.55$).

At 1 year, only 27% (4/15) of the CS patients and 20% (3/15) of the CS + CYC patients had proteinuria $\geqslant 1$ g/day, and no patient had nephrotic syndrome. At the end of the follow-up, median proteinuria was 0.2 g/day in both the groups ($P = 0.89$; Figure 2b).

By the end of the 1-year study, seven patients had became hypertensive for the first time (CS 2, CS + CYC 5), and at 1 year 14/19 (74%) CS patients and 12/17 (71%) CS + CYC patients were receiving renin–angiotensin system blockers.

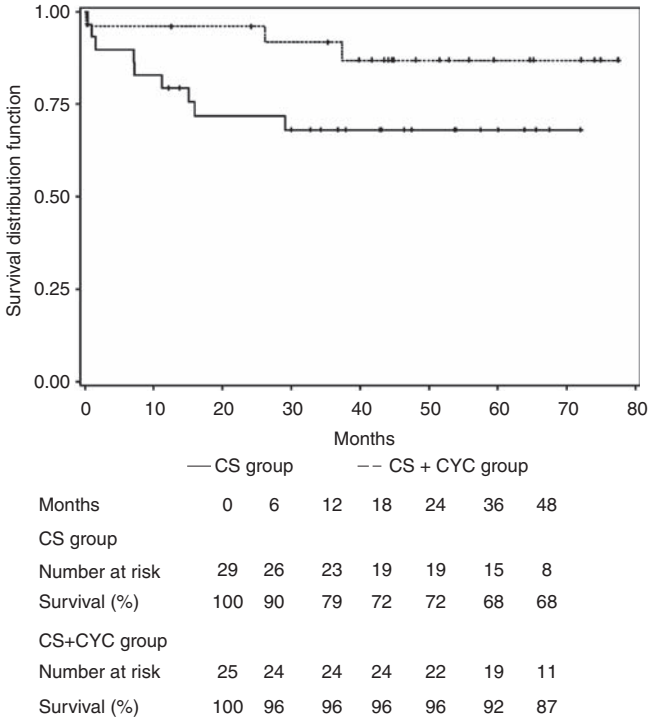
Safety

At M12, patient survival was 87% (95% confidence interval (CI) 79–95). Overall survival was not different between the two groups (CS group, 79% (95% CI 64–93) versus CS + CYC group, 96% (95% CI 89–100); $P = 0.08$, log-rank test) (Figure 3). As shown at M6 in Table 3, six CS patients died due to hemorrhagic shock ($n = 2$), end-stage liver disease ($n = 2$), and unknown causes, which was not related to the disease or its treatment ($n = 2$). In the CS + CYC group, one patient died of myocardial infarction, 6 days after study entry. The investigators did not relate any death either to HSP activity or to adverse events of the study drugs. At the end of the follow-up, the number of deaths did not differ significantly between the two groups (CS, 9; CS + CYC, 3; hazards ratio, 3.0, 95% CI 0.8–11.3; $P = 0.10$). Adjusted to the treatment arm by multivariable analysis, the BVAS at inclusion was the only parameter to show a statistically significant relationship with patient survival (hazards ratio, 2.4 for an increase of 10 BVAS points, 95% CI 1.4–4.5; $P = 0.003$).

Ten patients in the CS group experienced infections, one of whom required hospital admission. Seven patients in the CS + CYC group developed infections, none requiring hospital admission. Newly diagnosed diabetes or deterioration of pre-existing diabetes was reported in seven patients in the CS arm and six in the CS + CYC arm. Allocated treatment was discontinued before the end of the study for three patients of the CS group (lack of efficacy (two patients) and lost to follow-up) and four patients in the CS + CYC group (pregnancy, bladder tumor, lack of efficacy, and lost to follow-up).

DISCUSSION

Although several studies have investigated the treatment of HSP nephritis in children, no trial has previously been undertaken in adults. In this prospective, randomized trial we observed no benefit from addition of cyclophosphamide to steroid therapy for adult patients with severe HSP. It is unlikely that variations in the baseline characteristics would explain the lack of difference between the two treatment groups, as the result was unchanged after adjustment by logistic regression modeling. Indeed, only 54 patients could



Months	0	6	12	18	24	36	48
CS group							
Number at risk	29	26	23	19	19	15	8
Survival (%)	100	90	79	72	72	68	68
CS+CYC group							
Number at risk	25	24	24	24	22	19	11
Survival (%)	100	96	96	96	96	92	87

Figure 3 | Kaplan–Meier curves comparing patients receiving steroids alone (CS) or associated with cyclophosphamide (CS + CYC): survival from randomization to the end of follow-up. Adjusted to treatment arm by multivariable analysis, BVAS at inclusion was the only parameter to show a statistically significant relationship with patient survival (hazards ratio, 2.4 for an increase of 10 BVAS points, 95% CI 1.4–4.5; $P = 0.003$).

Table 3 | Number of patients experiencing adverse events during the 12-month study

	Steroids	Steroids+ cyclophosphamide
n	29	25
Adverse events		
Infection	10	7
Urinary tract	4	2
Necrotizing fasciitis	1	1
Zona zoster	0	1
Mycobacterium tuberculosis	1	0
Bronchitis	4	3
Diabetes[a]	7	6
Depression anxiety	2	2
Insomnia	3	0
Alopecia	1	1
Acne vulgaris/atrophia striata	0	1/1
Vertebral fracture		1
Deaths	*6*	*1*
Hemorrhagic shock	2	
Myocardial infarct		1
End-stage liver disease	2	
Unknown	2	

All tests are non-statistically significant at level 5%.
[a]Newly diagnosed or deterioration of pre-existing diabetes.

have been enrolled in the scheduled inclusion period. The stratification per center in combination with the small contribution of some centers resulted in this skewed distribution.

Our finding is in accordance with data from 'pediatric studies. A systematic review of 10 randomized, controlled trials in children concluded that of the few available therapies, only short-term prednisone improved renal outcome in pediatric HSP.[5] Some authors have even suggested that steroids, and more importantly, immunosuppressive drugs, offer no advantage in children with HSP nephritis.[6] A recent meta-analysis reported that early corticosteroid treatment in children reduces the risk that chronic renal disease will develop, although the robustness of their conclusions was limited by the small number of studies and patients, variable dosing regiments, and the degree of HSP severity.[7] Despite the lack of reliable evidence, we felt it to be unethical to include a placebo arm in this study.

Our findings also provide a prospective description of the course of severe HSP in adults. In our population, which was comparable to previously reported cohorts with regard to renal and extra-renal manifestations,[1,2,4,10–15] the short- and medium-term prognosis was good regardless of the treatment group. Both BVAS and proteinuria improved dramatically during the 1-year study regardless of the treatment group, and renal function remained stable after a median of ~ 5 years' follow-up. At the end of the follow-up no patient experienced extra-renal manifestation. Our patients can be regarded as having a positive outcome despite severe clinical features, as significant proteinuria (>1 g/day) and renal impairment were absent during follow-up, both of which are closely predictive of end-stage renal disease.[11–14] One possible explanation for this positive outcome is the use of renin–angiotensin system blockers in nearly all patients. A number of studies have shown a renoprotective effect for angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in IgA nephropathy.[16–18]

The BVAS reached zero (primary endpoint) in a very few number of patients, equally in both the groups. Of note, persisting microscopic hematuria, which is frequent in HSP nephritis and usually not considered as worse prognosis, counts 8 points in the BVAS score and accounts for the high score measured at 6 months in our population. At 6 months the patients showed no severe HSP manifestation, stable renal function, and proteinuria less than 1 g/day. However, more than half of them had a persisting microscopic hematuria. The extra-renal manifestations were then moderate, consisting of limited skin purpura on the legs in six patients (one only with necrotic lesions) and moderate arthralgia or abdominal pain in four patients. We speculate that the BVAS may not be optimal to evaluate HSP vasculitis activity. However, no score is currently available to quantify the activity in this specific vasculitis. Further study should define a new modified BVAS, suitable for HSP vasculitis.

No severe adverse events were reported in either group and no deaths were considered by the investigators to be related to HSP activity or to treatment-related adverse events. However, it was notable that the BVAS at baseline, adjusted to the treatment group, was the only factor, which showed a significant relationship with risk of death. The difference in the number of deaths between the two treatment groups could be attributed to the differences in the baseline characteristics (patients were significantly more severe in the CS group). We must also emphasize that the small number of patients included makes it difficult to draw any clear-cut conclusions. One could argue that a treatment group without steroid could have been included. Indeed, during the design of this study, such a possibility was raised but was not considered ethical by the investigators.

In summary, even though the relatively low number of patients does not permit definitive conclusions to be drawn, our results suggest that addition of cyclophosphamide provides no additional benefit for adults with severe HSP as compared with steroids alone. It is conceivable that even steroid therapy may not be indicated in such patients, but no treatment may be inappropriate in adult patients with severe HSP.

METHODS

Patients

Patients aged 18–84 years were eligible to take part in the study if they had a biopsy-proven diagnosis of HSP associated with severe involvement of one organ. HSP diagnosis was based on the Chapell Hill Nomenclature conference criteria,[19] that is, presence of one typical clinical manifestation (skin, gut, kidney, and/or joint) in conjunction with biopsy evidence of leukocytoclastic vasculitis with IgA deposition. Severe organ involvement could include renal biopsy-proven nephritis showing diffuse endocapillary proliferation (class-3) alone or with extra-capillary proliferation (class-4),[11] severe gastrointestinal involvement (gastrointestinal hemorrhage, ischemia, or perforation or abdominal pain persisting for more than 1 day and unresponsive to standard analgesics), pulmonary hemorrhage, cardiac or central nervous system involvement, and/or episcleritis.

Women of child-bearing potential were required to use one appropriate birth control method and were excluded from the study if they were pregnant or breastfeeding. Patients with other causes of purpura (thrombocytopenia, bacterial, or other forms of vasculitis) were excluded, as were patients infected by hepatitis-B and/or C viruses or HIV. Patients were also excluded if they had received immunosuppressants or steroids within the previous 2 weeks.

Study design

This multi-center, prospective, randomized, open-label trial included a 6-month treatment period with a further visit at M12. Data on mortality, end-stage renal disease, renal function, and daily proteinuria were collected up to the last follow-up. Randomization was performed centrally using a computer-generated random allocation sequence with blocks of random size. The investigators were informed of a patient's randomized group by telephone. As shown on Figure 4, all patients received intravenous methylprednisolone (7.5 mg/kg/day) for 3 days, followed by oral prednisone (initially 1 mg/kg/day for 1 week, and gradually tapering during the course of the study in the following manner: to 0.4 mg/kg/day at the end of the first month, 0.25 mg/kg/day at the end of the second

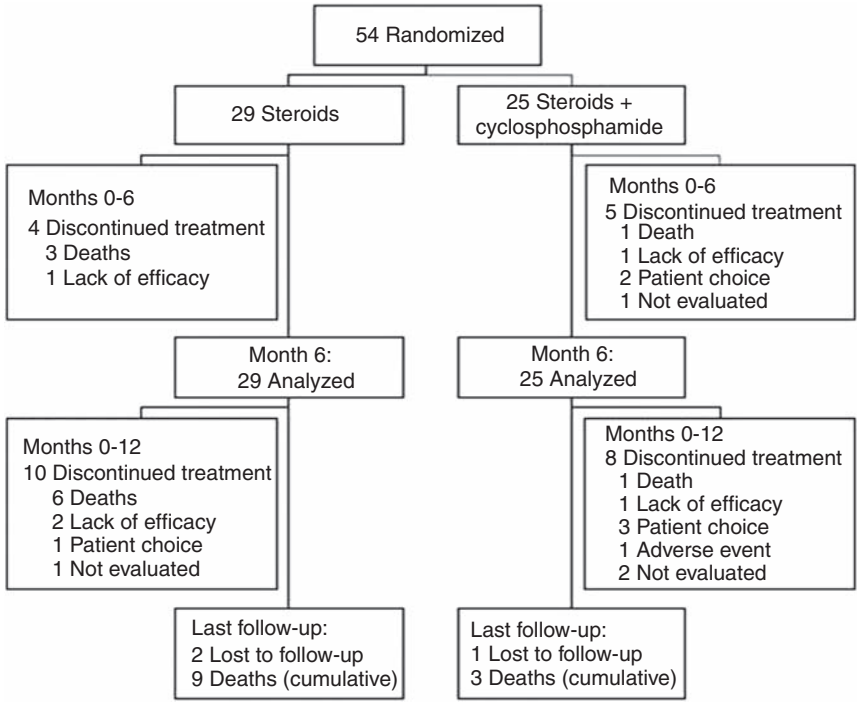


Figure 4 | Study design. All patients received intravenous methylprednisolone for 3 days, followed by oral prednisone. The patients were randomly assigned to receive, in addition to steroids, six pulses of intravenous cyclophosphamide.

month, and stopped at the end of the sixth month). The patients were randomly assigned to receive, in addition to steroids, intravenous cyclophosphamide (CS + CYC) at a dose of 0.6 g/m^2 on days 1 and 15, and at weeks 4, 8, 12, and 16, that is, six pulses in total. The dose was reduced according to renal function and not patient's age. The maximal dose was 1200 mg.

Physicians were encouraged to achieve a blood pressure lower than 125/75 mm Hg, favoring renin–angiotensin system blockers if proteinuria was present.

The study protocol was approved by the ethics review committee at each participating center and conducted according to the Declaration of Helsinki Principles. Written informed consent was obtained from all the patients.

Evaluation and study endpoints

Study visits took place on day 1 (the day of randomization), then monthly to M6, with a follow-up visit at M12. On day 1, evaluation comprised physical examination, skin biopsy of a new purpuric lesion with histological and immunofluorescence examination, and standard biological tests. Physical examination and biological tests, including blood pressure, creatinine, hematuria, and daily proteinuria, were repeated at each subsequent visit. The BVAS was recorded at all study visits. This score refers to new or worsening symptoms due to vasculitis activity, with higher scores indicating more active disease.[20] All adverse events were documented throughout the study, regardless of severity or relationship to treatment.

Renal biopsy was performed according to local practice at each center, usually prompted by renal failure and/or proteinuria >1 g/day. All renal biopsies were examined by two independent pathologists masked to the treatment assignment. On immunofluorescence, predominance of mesangial IgA among glomerular Ig deposits was required. All biopsies were classified according as follows: class-1, mesangiopathic GN; class-2, focal and segmental GN; class-3, endocapillary proliferative GN, and class-4, endocapillary and extra-capillary GN.[11] The proportion of glomeruli involved by global sclerosis was recorded. Interstitial fibrosis was scored according to the proportion of the parenchyma involved: none–mild (0–25%), moderate (25–50%), and severe (>50%).

The primary endpoint was complete disease remission at M6, defined as zero point on the BVAS with no persisting or new clinical and/or biological vasculitis. The secondary end points included renal function improvement at M12 compared with the baseline (defined as more than 50% increase in the eGFR (Cockcroft–Gault formula), daily proteinuria, occurrence of end-stage renal disease, death, and adverse events (particularly diabetes mellitus and infection)). Patient survival, end-stage renal failure, renal function, and daily proteinuria were also assessed on the basis of the data at the last follow-up.

Statistical analysis

The sample size calculation estimated that a population of 200 patients would have a statistical power of 80% to detect a significant difference in the primary endpoint between the two groups, using a two-sided test and a significance level of 5%, assuming an incidence of 50% in the CS group and 70% in the CS + CYC group. Due to slow recruitment only 54 patients were enrolled by the end of the scheduled 4-year inclusion period.

All analyses were performed on the basis of the intent-to-treat principle. The categorical variables are summarized as counts and percentages, and continuous variables as medians (ranges) or means (standard deviation) as appropriate. Missing BVAS results at 6 months were considered as failures in the primary endpoint analysis and were replaced by the last obtained value for the other

analyses. This replacement was chosen instead of multiple imputation because most of non-evaluated patients were deceased patients or treatment was stopped for inefficacy. Two patients stopped the trial at 3 months and one did not submit to the visit at M6 but was present at month 5. Categorical data were compared by using the χ^2-test or Fisher's exact test, and continuous variables were compared by using the Wilcoxon test or the Student's *t*-test. For the primary endpoint analysis, logistic regression modeling was used to adjust for baseline variables. Cox regression modeling was performed to study the relationship between treatment group, baseline variables (age, BVAS, hypertension, diabetes, and eGFR), and outcomes (death and end-stage renal disease) at the last follow-up. The paucity of events meant that only two independent variables could be included in the model, one of which was always the treatment arm. Results are expressed as hazard ratios with 95% CIs. All tests were two-tailed and a *P*-value less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed using SAS 9.1 (SAS Inc., Cary, NC, USA) for PC.

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DISCLOSURE

All the authors declared no competing interests.

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Clinical trial registration: This study has been registered in public trials registries (ClinicalTrials.gov), numbers NCT 00190229 and PHRC2001-AOM01034-P011014.

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Appendix

The CESAR study group

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